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### Response to antiplatelet treatment: from genes to outcome

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# Response to antiplatelet treatment: from genes to outcome

Dual antiplatelet therapy (aspirin plus clopidogrel) is the standard of care for patients with acute coronary syndrome who are managed medically or by percutaneous coronary intervention (PCI).<sup>1,2</sup> Clopidogrel has substantial benefit in patients undergoing PCI and stent implantation.<sup>1,2</sup> However, major adverse cardiovascular events, including stent thrombosis, can occur despite antiplatelet therapy, and a recent meta-analysis showed that persistent platelet reactivity on clopidogrel treatment confers a five-fold increased risk of major adverse cardiovascular events.<sup>3</sup>

Multiple chronic or transient mechanisms involved in high on-clopidogrel platelet reactivity have been identified: inadequate drug compliance, drug-drug interactions, age, diabetes, body-mass index, left-ventricle ejection function, and inflammation.<sup>4</sup> Platelet response to clopidogrel is highly heritable and not entirely explained by CYP2C19, an isoform of the cytochrome P450 involved in clopidogrel's metabolism, which suggests that further genetic variants in different genes play a pivotal role in determining individual susceptibility to antiplatelet drug response.<sup>4,5</sup> In 2007, the CYP2C19\*2 polymorphism was found to be associated with residual platelet reactivity in patients with acute coronary syndrome who were undergoing PCI on antiplatelet treatment.<sup>6</sup> Successively, in different clinical settings and at different follow-up, CYP2C19\*2 and other allelic variants in this gene were shown to be independent determinants of major adverse cardiovascular events in patients on clopidogrel.<sup>4,7,8</sup> In May, 2009, the US Food and Drug Administration recommended the change to clopidogrel's prescribing label to reflect these findings.<sup>9</sup>

New P2Y<sub>12</sub>-receptor antagonists are now available. Prasugrel is a third-generation thienopyridine associated with greater active metabolite generation, superior inhibition of ADP-induced platelet aggregation, and less response variability than with clopidogrel.<sup>10</sup> In the TRITON-TIMI 38 trial of patients with acute coronary syndrome who were undergoing PCI, the prevalence of cardiovascular death, non-fatal myocardial infarction, or stroke was lower with prasugrel than with clopidogrel.<sup>11</sup> However, rates of bleeding were higher in the prasugrel group.

The novel antiplatelet agent ticagrelor was also evaluated against clopidogrel in patients with acute

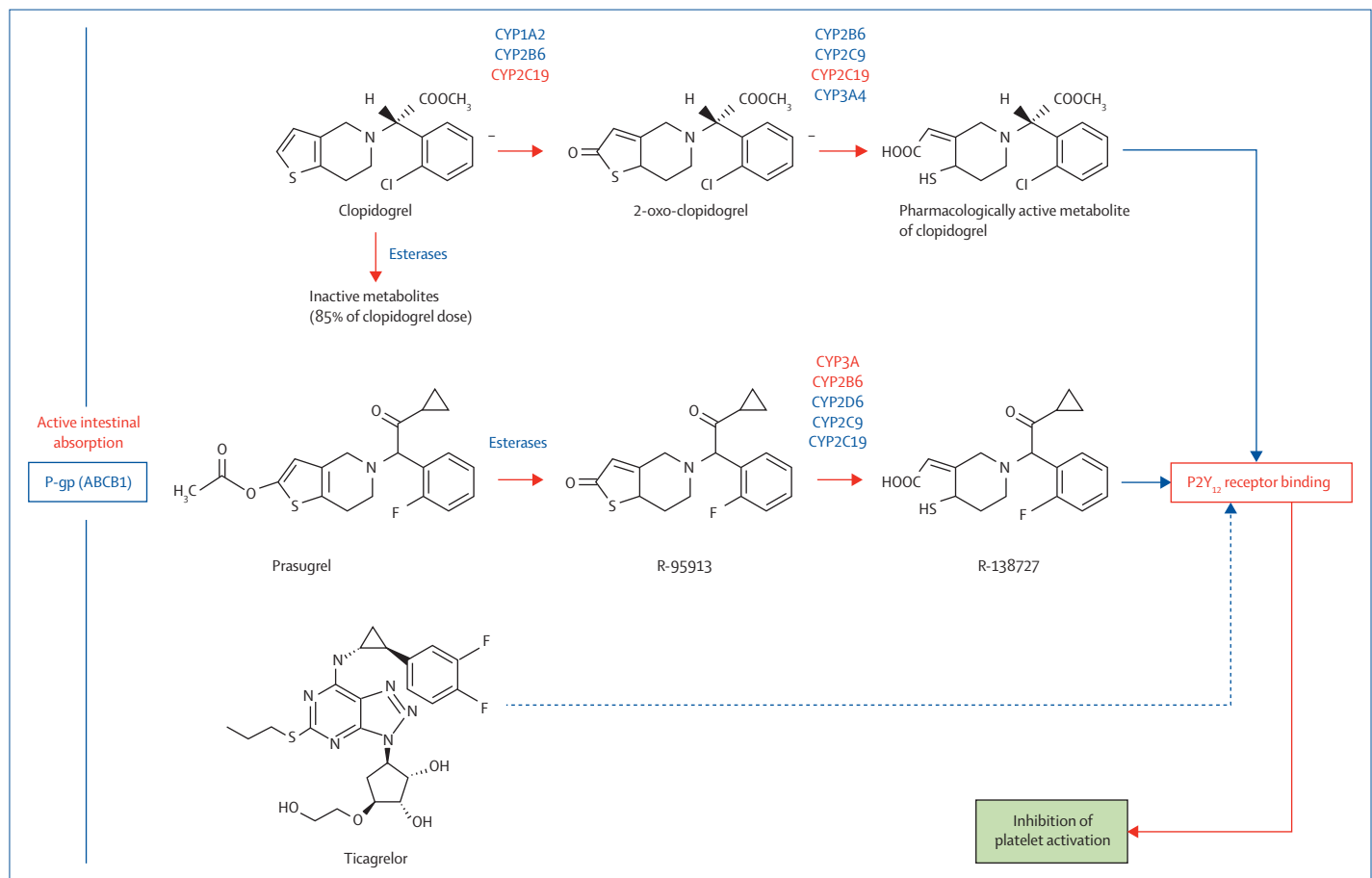
coronary syndrome in the PLATO trial.<sup>12</sup> Ticagrelor was associated with significant reduction in cardiovascular death, myocardial infarction, and stroke, without any difference in the overall incidence of major bleeding, but with an increase in major bleeding related to non-coronary-artery bypass graft.

The issue of the optimum dose of clopidogrel and/or the personalisation of alternative antiplatelet therapeutic strategies aimed at reducing ischaemic events and minimisation of bleedings is open. We think that the relevance of obtaining an "adequate residual platelet reactivity" on antiplatelet treatment is now well founded and the crucial goal is now to identify the clinical, environmental, procedural, and genetic determinants of the increased risk of major adverse cardiovascular events and of bleedings in these high-risk patients.

In *The Lancet* today, Jessica Mega<sup>13</sup> and Lars Wallentin,<sup>14</sup> and their respective colleagues, have addressed the important issue of finding further genetic variants beside those in CYP2C19 and beside the other clinical and procedural risk factors associated with major adverse cardiovascular events in patients with acute coronary syndrome who are on antiplatelet therapy. Both papers confirmed the independent role of the CYP2C19 loss-of-function alleles as a determinant of major adverse cardiovascular events in these patients on clopidogrel, even if with a lower impact in PLATO than in TRITON-TIMI-38 or in the recent meta-analyses,<sup>7,8</sup> whereas they did not show any effects of CYP2C19 genetic variants in patients on prasugrel<sup>13</sup> or ticagrelor.<sup>14</sup>

The most interesting novel data from these two papers<sup>12,13</sup> are those about the role of the 3435C→T polymorphism in ABCB1, a gene coding the P-glycoprotein involved in drug absorption, on the efficacy of the three different antiplatelet treatments. Previous data, from patients presenting with an acute myocardial infarction in a nationwide French registry and receiving clopidogrel, showed that patients with two ABCB1 variant alleles (3435 TT genotype) had a higher rate of cardiovascular events at 1 year than did those with the 3435 CC genotype.<sup>15</sup> However, in that study, the ABCB1 polymorphism was not an independent predictor of outcome in the subgroup of patients undergoing percutaneous coronary intervention.<sup>14</sup> For the ABCB1 polymorphism, even

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**Figure: Mechanism of action and metabolic pathways for clopidogrel, prasugrel, and ticagrelor**

All three drugs are absorbed intestinally. In this step, P-glycoprotein, encoded ABCB1, could intervene. Clopidogrel is mostly hydrolysed by esterases to inactive carboxylic acid derivative that accounts for 85% of clopidogrel-related circulating compounds. Several cytochrome P450 (CYP450) enzyme isoforms are responsible for oxidation of thiophene ring of clopidogrel to 2-oxo-clopidogrel, which is further oxidised by other CYP450 isoforms to result in opening of the thiophene ring and formation of carboxyl and thiol groups. Thiol group irreversibly binds to ADP P2Y<sub>12</sub> receptor expressed on platelet surface and causes irreversible blockade of ADP binding. Prasugrel is rapidly hydrolysed by carboxyesterases to a thiolactone (R-95913), which is subsequently metabolised to the prasugrel-active metabolite, R-138727. Conversion of R-95913 to R-138727 is catalysed by several CYP450 enzymes, with greatest contributions from CYP3A and CYP2B6, lesser contributions from CYP2C9 and CYP2C19, and even less from CYP2D6. Active metabolite of prasugrel irreversibly binds to ADP P2Y<sub>12</sub> receptor. Unlike the other two thienopyridines, ticagrelor does not need to be converted by liver into active metabolite, and is a reversible ADP-receptor antagonist. P-gp=P-glycoprotein. ABCB1=ATP-binding cassette sub-family B member 1. Dotted arrow=no liver conversion and reversible binding to P2Y<sub>12</sub> receptor.

though both studies investigated relatively large populations, Mega and colleagues and Wallentin and colleagues obtained contrasting results. Mega and colleagues found that patients on clopidogrel who had the ABCB1 3435 TT genotype were at increased risk of recurrent ischaemic events, probably due to less platelet inhibition according to their observations in healthy individuals. On the other hand, Wallentin and colleagues observed a numerically higher rate of primary efficacy events for the high-expression group (patients with the ABCB1 3435 CC genotype) who were on clopidogrel.

Interpreting the results from the two studies, we should consider that several important differences occur or are not deeply valuable—eg, clinical setting

(in the PLATO cohort, only two-thirds of patients were managed invasively), severity of disease, available clinical information, geographic origin, and percentage of platelets naive to antiplatelet treatment. On the other hand, few and contrasting data are available on the possible effect of the 3435C→T ABCB1 polymorphism on clopidogrel's absorption or metabolism.<sup>16-18</sup>

The fact that prasugrel's and ticagrelor's efficacy was not influenced by CYP2C19 and ABCB1 polymorphisms does not mean that other polymorphisms in different genes (eg, CYP3A4 or CYP3A5) could not affect their pharmacodynamics and pharmacokinetics. In fact, on the basis of available knowledge, CYP2C19 and ABCB1 have a marginal or no role on prasugrel's and ticagrelor's metabolism and absorption.

The temptation to find the easier way by choosing the “superior” drug on the basis of large trials in which participants with different risk profiles venture to be considered equal is not desirable. The issue is not to choose the lesser of the evils, but the better of the goods—by identifying the therapeutic strategy that, in consideration of individual characteristics, warrants the higher benefit/risk ratio. Evaluation of the best management should also take into account the clinical determinants of platelet reactivity—from age and sex to body-mass index, diabetes, and inflammation—which might modulate platelet function, while also considering the timing from the acute event, as shown by the CURRENT-OASIS 7 study.<sup>19</sup>

For this purpose, starting from these experiences, the scientific community should draw the indications to standardise experimental designs. Prospective studies evaluating different antiplatelet treatments tailored to individual characteristics of patients—genetic profile, residual platelet reactivity, drug–drug interactions, and traditional and procedural risk factors—are urgently needed to identify therapeutic strategies that will provide the best benefit for the single patient in this high-risk clinical setting.

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